Brian G. Kingwell
bgkingwell@smart-biggar.ca

Vancouver file no. 80021-185

20 August 2001

VIA FACSIMILE/MAIL 011 49 89 2399 4465

PCT Chapter II
MU DG 2

European Patent Office
International Preliminary Examining Authority
Erhardstrasse 27
D-80298 Munich
GERMANY

Attention: Pa I Soto, R.
Authorized Officer/Examiner

Dear Sirs:

Re: International Application PCT/CA00/00762

Title:	LPL VARIANT THERAPEUTICS
Applicant:	THE UNIVERSITY OF BRITISH COLUMBIA *et al.*
Int'l Filing Date:	23 June 2000
Priority Date:	24 June 1999

This is in response to the Written Opinion dated 29 March 2001, and further to our letters of 22 June and 13 July 2001.

REMARKS

The Examiner has acknowledged that claims 1-33 define subject matter that is new, in accordance with the requirement of Art. 33(2) PCT. The Examiner has objected to the claims as lacking an inventive step, on the basis of D1 and D2 in combination.

The test for establishing inventive step is whether the prior art demonstrates that there was **a reasonable expectation of success** in making and using the claimed

invention. This test has for example been set out by the EPO Board of Appeal in T 296-93, "HBV antigen production/ BIOGEN", EP- B1 182 442 (not yet published in the OJ EPO), as follows:

> "The fact that other persons (or teams) were also working on the same project might suggest that it was 'obvious to try' or that it was 'an interesting area to explore', but it does not necessarily imply that there was "a reasonable expectation of success". "A reasonable expectation of success", which should not be confused with the understandable "hope to succeed", implies the ability of the skilled person to reasonably predict, on the basis of the existing knowledge before the starting of a research project, a successful conclusion to the said project within acceptable time limits. The more unexplored a technical field of research is, the more difficult is the making of predictions about its successful conclusion and, consequently, the lower the expectation of success."

In the present case, the demonstration in the present application that the administration of an LPL S447X therapeutic produces a therapeutically relevant response *in vivo* (see Examples 1 and 2 of the present application) represents a significant breakthrough in this area of research, for which there was no reasonable expectation of success in view of the cited references or other prior art. The prior art (particularly D2) merely reports an association between the LPL S447X allele and certain disease outcomes, it does not serve as a sufficient basis for a **reasonable expectation of success** through the use of an LPL S447X therapeutic. The Applicants respectfully submit that the physiology of cardiovascular disease and lipid metabolism is sufficiently complex that one could not have known with any degree of certainty what the effect would be of administering an LPL S447X therapeutic to an animal, prior to the discoveries reported in the present application demonstrating the *in vivo* effects of such therapeutics.

The extent to which the present results were **not** predictable is for example shown by the cited art itself. In particular, **D2** discloses that post-heparin LPL relationships to lipids and lipoproteins were not altered by apo E genotypes, whereas **D1** indicates that apo E is one of the alternative proteins that may be used in the treatment of

cardiovascular disease (see D2 Abstract and D1, page 9, lines 29-36). Irrespective of whether apo E therapeutics may be effective or not, this demonstrates the considerable amount of uncertainty regarding the actual therapeutic effect of any one component involved in regulating the complex balance of plasma lipids and lipoproteins in cardiovascular disease. D1 and D2 in combination therefore reinforce the general teaching in the art that there can be no **reasonable expectation of success** in modulating physiological conditions relevant to cardiovascular disease, in the absence of experimental evidence such as is provided in the present application showing that a particular therapeutic can actually be effective *in vivo*. Examples 1 and 2 in the present application provide, for the first time, *in vivo* evidence of the surprising effects of LPL S447X therapeutics. The degree of unpredictability of this result is reinforced by the surprisingly different results reported for the LPL S447X therapeutics compared to the wild type LPL protein controls in these Examples.

The present application reports the surprising result that the LPL S447X therapeutics of the invention may be used to provide an increase in LPL protein mass in post-heparin plasma ***in vivo***. This is a result which must be the consequence of a complex and multifaceted interaction between the LPL S447X therapeutic and a wide variety of factors that together help to regulate this physiological outcome which is relevant to cardiovascular disease. Any number of endogenous regulatory mechanisms could have been engaged by the administration of the LPL S447X therapeutic to prevent this result from occurring. Even with the teaching of D1 and D2, one skilled in the art could not have had a **reasonable expectation** that a LPL S447X therapeutic would **successfully** modulate LPL protein mass in post-heparin plasma, and could not therefore have had a reasonable expectation of success with the presently claimed invention. The only reasonable basis for such an expectation is the experimental evidence presented in the application.

In view of the foregoing submissions, Applicants respectfully submit that the claimed invention is novel, involves an inventive step and is industrially applicable. Applicant requests that any remaining reservations that the examiner may have should be discussed with the undersigned in a personal interview, under Rule 66.6, or be made the

subject of an additional Written Opinion to which the applicant may respond under Rule 66.4.

Respectfully submitted,

SMART & BIGGAR

Brian G. Kingwell
Phone: (604) 682-7780
Fax: (604) 682-0274

BGK:seb

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00220 A3

(51) International Patent Classification[7]: A61K 38/46, 48/00, C12N 15/63, A61P 9/10 // C12N 9/20

(21) International Application Number: PCT/CA00/00762

(22) International Filing Date: 23 June 2000 (23.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
99202048.7 24 June 1999 (24.06.1999) EP

(71) Applicants *(for all designated States except US)*: **THE UNIVERSITY OF BRITISH COLUMBIA** [CA/CA]; University-Industry Liaison Office, IRC Building, Room 331, 2194 Health Sciences Mall, Vancouver, British Columbia V6T 1Z3 (CA). **AMSTERDAM MOLECULAR THERAPEUTICS B.V. (AMT)** [NL/NL]; Meibergdreef 61, NL-1105 BA Amsterdam (NL). **ACADEMIC HOSPITAL AT THE UNIVERSITY OF AMSTERDAM** [NL/NL]; Meibergdreef 9, NL-1105 AZ Amsterdam (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HAYDEN, Michael, R.** [CA/CA]; 4464 West 7th Avenue, Vancouver, British Columbia V6R 1W9 (CA). **KASTELEIN, John, J., P.** [NL/NL]; Hauwert 141, NL-1691 EE Hauwert (NL).

(74) Agents: KINGWELL, Brian, G. et al.; Smart & Biggar Vancouver Centre, Suite 2200, Box 11560, 650 West Georgia Street, Vancouver, British Columbia V6B 4N8 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publication of the international search report: 12 July 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/00220 A3

(54) Title: LIPOPROTEIN LIPASE (LPL) VARIANT THERAPEUTICS

(57) Abstract: The invention provides for the use of a therapeutic derived from a truncated lipoprotein lipase protein (LPL S447X), including nucleic acids encoding such proteins, for the treatment of conditions including LPL responsive conditions, such as cardiovascular disease, hypertension, LPL deficiency, high triglyceride levels, low HDL-cholesterol levels or atherosclerosis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00762

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/46 A61K48/00 C12N15/63 A61P9/10 //C12N9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 27512 A (BAYLOR COLLEGE MEDICINE) 19 October 1995 (1995-10-19) page 9, line 29 -page 11, line 26; examples 11-15	1-34
Y	HENDERSON H E ET AL: "Lipoprotein lipase activity is decreased in a large cohort of patients with coronary artery disease and is associated with changes in lipids and lipoproteins." JOURNAL OF LIPID RESEARCH, vol. 40, no. 4, April 1999 (1999-04), pages 735-743, XP002158083 the whole document	1-34

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	06/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Teyssier, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00762

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	FISHER R M ET AL: "Common variation in the lipoprotein lipase gene: Effects on plasma lipids and risk of atherosclerosis." ATHEROSCLEROSIS, vol. 135, no. 2, December 1997 (1997-12), pages 145-159, XP000978943 the whole document	1-34

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Internal Application No
PCT/CA 00/00762

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9527512 A	19-10-1995	AU 695618 B	20-08-1998
		AU 2283495 A	30-10-1995
		AU 716148 B	17-02-2000
		AU 9405498 A	14-01-1999
		CA 2188675 A	19-10-1995
		EP 0755268 A	29-01-1997

14

REC'D 19 SEP 2001
WIPO PCT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80021-185		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00762	23/06/2000	24/06/1999
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant THE UNIVERSITY OF BRITISH COLUMBIA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/01/2001	17.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pa l Soto, R Telephone No. +49 89 2399 7346

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00762

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-33 as originally filed

Claims, No.:

1-34 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

Sequence listing part of the description, pages:

1-8, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 11-20 (industrial applicability); and 34.

because:

   ☒ the said international application, or the said claims Nos. 11-20 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 34 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard t nov lty, inv ntive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10 and 21-33; for 11-20 see separate sheet
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 11-20** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Present **claim 34** does not meet the requirements of Art. 6 because it does not define the matter for which protection is sought. This should be achieved in terms of technical features and not by references to the description and/or the drawings. Furthermore, according to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here. No opinion has been established with respect to novelty, inventive step and industrial applicability of said claim.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Reference is made to the following documents:

   D1: WO 95 27512 A (BAYLOR COLLEGE MEDICINE) 19 October 1995,
   D2: HENDERSON H. E. ET AL: 'Lipoprotein lipase activity is decreased in a large cohort of patients with coronary artery disease and is associated with changes in lipids and lipoproteins.' JOURNAL OF LIPID RESEARCH, vol. 40, no. 4, April 1999, pages 735-743, and
   D3: FISHER R. M. ET AL: 'Common variation in the lipoprotein lipase gene: Effects on plasma lipids and risk of atherosclerosis.' ATHEROSCLEROSIS, vol. 135, no. 2, December 1997, pages 145-159.

4. The present application relates to **(i)** the use of an LPL S447X therapeutic for the preparation of a pharmaceutical composition for the treatment of an LPL-responsive

condition in a subject (**claim 1**); **(ii)** a method of treating a disease in a subject, comprising administering to the subject an effective amount of an LPL S447X therapeutic, wherein the disease is an LPL-responsive disease (**claim 11**); **(iii)** an LPL S447X therapeutic for use as an active pharmaceutical substance wherein the LPL S447X therapeutic is an LPL S447X protein, as specified in **claim 21,** or an LPL S447X nucleic acid encoding said LPL S447 X protein; and **(iv)** a gene therapy vector comprising an LPL S447X therapeutic as specified before (**claim 28**).

5. The present application satisfies the requirements of Art. 33(2) PCT because **th subject-matter of claims 1-33 is new**. None of the documents cited in the International search report discloses all the technical features of the independent claims of the present application.

6. The present application does also meet the requirements of Art. 33(3) PCT because **the subject-matter of claims 1-33 involves an inventive step**.

D1 (see paragraph linking pages 9 and 10, lines 20-26 on page 11, example 11 and claims 24-25), which is regarded as the closest prior art, discloses a method of gene therapy for the treatment of cardiovascular disease based in the overexpression of lipoprotein lipase (LPL). The present application differs from **D1** in that the therapeutic agent is LPL S447X instead of the wild type LPL. The use of LPL S447X provides advantageous results as compared to the wild type LPL.

The **problem** to be solved by the present application is regarded in the provision of a more effective gene therapy than that disclosed in **D1** for the treatment of cardiovascular disease and other conditions requiring an elevation of LPL levels.

The **solution** provided by the present application is considered as involving an inventive step for the following reasons. **D2** (see the abstract and right column on page 741) discloses that the S447X gene variant is associated with an increase in LPL activity when compared to the wild type LPL. **D3** (see section 5.3.) reports that the S447X mutation is associated with a beneficial lipid profile with lower TG concentrations and protection against CAD. It also reports *in vitro* studies suggesting that the increase in post-heparin LPL activity is due to a higher production of LPL-S447X. These indications would probably prompt the skilled person to try a

modification of the solution disclosed in **D1** in the way proposed in the present application in order to solve the problem posed. However, it is considered that the physiology of cardiovascular disease and lipid metabolism is sufficiently complex to have predicted, prior to the discoveries reported in the present application, what the effect would have been of administering an LPL S447X therapeutic in connection with cardiovascular disease and LPL-responsive conditions, in general. Thus, the reports in the prior art do not serve as a sufficient basis for a reasonable expectation of success through the use of an LPL S447X therapeutic.

7. For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (present claims 11-20), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

8. Claims 28-33 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

Re Item VIII

C rtain observations on the international application

9. The technical features of present claims 5-6, 15-16, 23-24 and 30-31 are not mentioned in the description as required by Art. 6 PCT (see the Guidelines CIII, 6.6.).

10. Present **claims 3, 7, 13, 17, 21, 25, 28 and 32,** as well as those claims depending or relating to them, **do not meet the requirements of Art. 6 PCT** in that the matter for which protection is sought is not clearly defined. The reason is that said claims include in their formulation the expression "contiguous segment", which has no recognised meaning in the art, whereby the corresponding LPL S447 protein is not clearly defined.

11. Present **claims 6, 16, 24 and 31** also fail to clearly define the matter for which protection is sought because the expression "stringent conditions" is vague and has not recognised meaning in the art. Thus, said claims **do also not meet th requirements of Art. 6 PCT**.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

2001 SEP 25 P 12:39

KINGWELL, Brian G.
SMART & BIGGAR
Vancouver Centre, Suite 2200
650 W. Georgia Street
P.O. Box 11560
Vancouver, BC V6B 4N8
CANADA

SMART & BIGGAR
650 WEST GEORGIA STREET
VANCOUVER, B.C.

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference 80021-185	Date of mailing *(day/month/year)* 17.09.2001
	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00762	23/06/2000	24/06/1999

Applicant
THE UNIVERSITY OF BRITISH COLUMBIA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80021-185		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00762	23/06/2000	24/06/1999
International Patent Classification (IPC) or national classification and IPC A61K38/00		
Applicant THE UNIVERSITY OF BRITISH COLUMBIA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/01/2001	17.09.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Pa l Soto, R Telephone No. +49 89 2399 7346

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00762

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-33 as originally filed

Claims, No.:

1-34 as originally filed

Drawings, sheets:

1/3-3/3 as originally filed

Sequence listing part of the description, pages:

1-8, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 11-20 (industrial applicability); and 34.

because:

   ☒ the said international application, or the said claims Nos. 11-20 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 34 are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00762

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-33
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-10 and 21-33; for 11-20 see separate sheet
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 11-20** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Present **claim 34** does not meet the requirements of Art. 6 because it does not define the matter for which protection is sought. This should be achieved in terms of technical features and not by references to the description and/or the drawings. Furthermore, according to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here. No opinion has been established with respect to novelty, inventive step and industrial applicability of said claim.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Reference is made to the following documents:

   D1: WO 95 27512 A (BAYLOR COLLEGE MEDICINE) 19 October 1995,
   D2: HENDERSON H. E. ET AL: 'Lipoprotein lipase activity is decreased in a large cohort of patients with coronary artery disease and is associated with changes in lipids and lipoproteins.' JOURNAL OF LIPID RESEARCH, vol. 40, no. 4, April 1999, pages 735-743, and
   D3: FISHER R. M. ET AL: 'Common variation in the lipoprotein lipase gene: Effects on plasma lipids and risk of atherosclerosis.' ATHEROSCLEROSIS, vol. 135, no. 2, December 1997, pages 145-159.

4. The present application relates to **(i)** the use of an LPL S447X therapeutic for the preparation of a pharmaceutical composition for the treatment of an LPL-responsive

condition in a subject (**claim 1**); **(ii)** a method of treating a disease in a subject, comprising administering to the subject an effective amount of an LPL S447X therapeutic, wherein the disease is an LPL-responsive disease (**claim 11**); **(iii)** an LPL S447X therapeutic for use as an active pharmaceutical substance wherein the LPL S447X therapeutic is an LPL S447X protein, as specified in **claim 21,** or an LPL S447X nucleic acid encoding said LPL S447 X protein; and **(iv)** a gene therapy vector comprising an LPL S447X therapeutic as specified before (**claim 28**).

5. The present application satisfies the requirements of Art. 33(2) PCT because **the subject-matter of claims 1-33 is new**. None of the documents cited in the International search report discloses all the technical features of the independent claims of the present application.

6. The present application does also meet the requirements of Art. 33(3) PCT because **the subject-matter of claims 1-33 involves an inventive step**.

D1 (see paragraph linking pages 9 and 10, lines 20-26 on page 11, example 11 and claims 24-25), which is regarded as the closest prior art, discloses a method of gene therapy for the treatment of cardiovascular disease based in the overexpression of lipoprotein lipase (LPL). The present application differs from **D1** in that the therapeutic agent is LPL S447X instead of the wild type LPL. The use of LPL S447X provides advantageous results as compared to the wild type LPL.

The **problem** to be solved by the present application is regarded in the provision of a more effective gene therapy than that disclosed in **D1** for the treatment of cardiovascular disease and other conditions requiring an elevation of LPL levels.

The **solution** provided by the present application is considered as involving an inventive step for the following reasons. **D2** (see the abstract and right column on page 741) discloses that the S447X gene variant is associated with an increase in LPL activity when compared to the wild type LPL. **D3** (see section 5.3.) reports that the S447X mutation is associated with a beneficial lipid profile with lower TG concentrations and protection against CAD. It also reports *in vitro* studies suggesting that the increase in post-heparin LPL activity is due to a higher production of LPL-S447X. These indications would probably prompt the skilled person to try a

modification of the solution disclosed in **D1** in the way proposed in the present application in order to solve the problem posed. However, it is considered that the physiology of cardiovascular disease and lipid metabolism is sufficiently complex to have predicted, prior to the discoveries reported in the present application, what the effect would have been of administering an LPL S447X therapeutic in connection with cardiovascular disease and LPL-responsive conditions, in general. Thus, the reports in the prior art do not serve as a sufficient basis for a reasonable expectation of success through the use of an LPL S447X therapeutic.

7. For the assessment of the present claims 1-27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment (present claims 11-20), but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

8. Claims 28-33 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

Re Item VIII

Certain observations on the international application

9. The technical features of present claims 5-6, 15-16, 23-24 and 30-31 are not mentioned in the description as required by Art. 6 PCT (see the Guidelines CIII, 6.6.).

10. Present **claims 3, 7, 13, 17, 21, 25, 28 and 32,** as well as those claims depending or relating to them, **do not meet the requirements of Art. 6 PCT** in that the matter for which protection is sought is not clearly defined. The reason is that said claims include in their formulation the expression "contiguous segment", which has no recognised meaning in the art, whereby the corresponding LPL S447 protein is not clearly defined.

11. Present **claims 6, 16, 24 and 31** also fail to clearly define the matter for which protection is sought because the expression "stringent conditions" is vague and has not recognised meaning in the art. Thus, said claims **do also not meet the requirements of Art. 6 PCT**.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
80021-185		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00762	23/06/2000	24/06/1999
Applicant		
THE UNIVERSITY OF BRITISH COLUMBIA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

LIPOPROTEIN LIPASE (LPL) VARIANT THERAPEUTICS

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00762

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/46 A61K48/00 C12N15/63 A61P9/10 //C12N9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 27512 A (BAYLOR COLLEGE MEDICINE) 19 October 1995 (1995-10-19) page 9, line 29 -page 11, line 26; examples 11-15 ---	1-34
Y	HENDERSON H E ET AL: "Lipoprotein lipase activity is decreased in a large cohort of patients with coronary artery disease and is associated with changes in lipids and lipoproteins." JOURNAL OF LIPID RESEARCH, vol. 40, no. 4, April 1999 (1999-04), pages 735-743, XP002158083 the whole document --- -/--	1-34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2001	06/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Teyssier, B

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	FISHER R M ET AL: "Common variation in the lipoprotein lipase gene: Effects on plasma lipids and risk of atherosclerosis." ATHEROSCLEROSIS, vol. 135, no. 2, December 1997 (1997-12), pages 145-159, XP000978943 the whole document	1-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/00762

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9527512 A	19-10-1995	AU 695618 B	20-08-1998
		AU 2283495 A	30-10-1995
		AU 716148 B	17-02-2000
		AU 9405498 A	14-01-1999
		CA 2188675 A	19-10-1995
		EP 0755268 A	29-01-1997